Chapter 14: Basic Radiobiology

Set of 88 slides based on the chapter authored by N. Suntharalingam, E.B. Podgorsak, J.H. Hendry of the IAEA publication:
Radiation Oncology Physics: A Handbook for Teachers and Students

Objective:

To familiarize the student with the basic principles of radiobiology.

IAEA
International Atomic Energy Agency

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14.1 INTRODUCTION

- Radiobiology is a branch of science which combines the basic principles of physics and biology and is concerned with the action of ionizing radiation on biological tissues and living organisms.
- The study of basic radiobiological mechanisms deals with biological effects produced by energy absorption in small volumes corresponding to single cells or parts of cells.

14.1 INTRODUCTION

- All living entities are made up of protoplasm, which consists if inorganic and organic compounds dissolved or suspended in water.
- The smallest unit of protoplasm capable of independent existence is the cell, the basic microscopic unit of all living organisms.

14.1 INTRODUCTION

- A group of cells that together perform one or more functions is referred to as tissue.
- A group of tissues that together perform one or more functions is called an organ.
- A group of organs that perform one or more functions is an organ system or an organism.

14.1 INTRODUCTION

- Cells contain:
  - Inorganic compounds (water and minerals)
  - Organic compounds (proteins, carbohydrates, nucleic acids, lipids)
- The two main constituents of a cell are the cytoplasm and the nucleus:
  - Cytoplasm supports all metabolic functions within a cell.
  - Nucleus contains the genetic information (DNA).

14.1 INTRODUCTION

- Human cells are either somatic cells or germ cells.

  The germ cells are either a sperm or an egg, all other human cells are called the somatic cells.

- Cells propagate through division:
  - Division of somatic cells is called mitosis and results in two genetically identical daughter cells.
  - Division of germ cells is called meiosis and involves two fissions of the nucleus giving rise to four sex cells, each possessing half the number of chromosomes of the original germ cell.

14.1 INTRODUCTION

- When a somatic cell divides, two cells are produced, each carrying a chromosome complement identical to that of the original cell.
- The new cells themselves may undergo further division, and the process continues producing a large number of progeny.

14.1 INTRODUCTION

- A chromosome is a microscopic, threadlike part of a cell that carries hereditary information in the form of genes.
- Every species has a characteristic number of chromosomes; humans have 23 pairs (22 pairs are non-sex chromosomes and 1 pair is sex chromosome).
- A gene is a unit of heredity that occupies a fixed position on a chromosome.

14.1 INTRODUCTION

- Somatic cells are classified as:
  - Stem cells, which exists to self-perpetuate and produce cells for a differentiated cell population.
  - Transit cells, which are cells in movement to another population.
  - Mature cells, which are fully differentiated and do not exhibit mitotic activity.

14.2 CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

- Radiation is classified into two main categories:
  - Non-ionizing radiation (cannot ionize matter)
  - Ionizing radiation (can ionize matter)
- Ionizing radiation contains two major categories
  - Directly ionizing radiation (charged particles)
    electrons, protons, alpha particles, heavy ions
  - Indirectly ionizing radiation (neutral particles)
    photons (x rays, gamma rays), neutrons

14.2 CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

- In radiobiology and radiation protection the linear energy transfer (LET) is used for defining the quality of an ionizing radiation beam.
- In contrast to the stopping power, which focuses attention on the energy loss by a charged particle moving through a medium, the LET focuses attention on the linear rate of energy absorption by the absorbing medium as the charged particle traverses the medium.

14.2 CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

- The ICRU defines the LET as follows:

  "LET of charged particles in a medium is the quotient $dE/d\ell$ where dE is the average energy locally imparted to the medium by a charged particle of specified energy in traversing a distance of $d\ell$."

14.2 CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

- In contrast to the stopping power, which has a typical unit of MeV/cm, the unit reserved for the LET is keV/μm.
- The energy average is obtained by dividing the particle track into equal energy increments and averaging the length of track over which these energy increments are deposited.

14.2 CLASSIFICATION OF RADIATIONS IN RADIOBIOLOGY

- Typical LET values for commonly used radiations are:

Radiation	LET (keV/μm)
250 kVp X rays	2
Cobalt-60 γ rays	0.3
3 MeV X rays	0.3
1 MeV electrons	0.25

- LET values for other, less common radiations are:

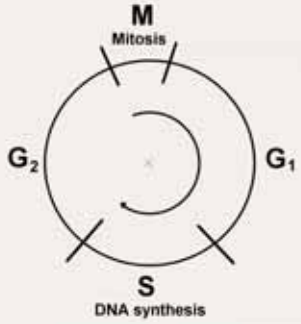
Radiation	LET (keV/μm)
14 MeV neutrons	12
Heavy charged particles	100 - 200
1 keV electrons	12.3
10 keV electrons	2.3

14.3 CELL CYCLE AND CELL DEATH

- The cell proliferation cycle is defined by two time periods:
  - Mitosis M, where division takes place.
  - The period of DNA synthesis S.
- The S and M portions of the cell cycle are separated by two periods (gaps) G_1 and G_2 when, respectively
  - DNA has not yet been synthesized.
  - Has been synthesized but other metabolic processes are taking place.

14.3 CELL CYCLE AND CELL DEATH

- The time between successive divisions (mitoses) is called the cell cycle time.
- The cell cycle time for mammalian cells is of the order of 10 - 20 hours:
  - The S phase is usually in the range of 6 - 8 hours.
  - The M phase is less than 1 hour.
  - G_2 is in the range of 2 - 4 hours.
  - G_1 is in the range of 1 - 8 hours.



The stages of the mitotic cell cycle
M = mitosis
S = DNA synthesis
G_1 and G_2 = gaps

14.3 CELL CYCLE AND CELL DEATH

- The cell cycle time for stem cells in certain tissues is up to 10 days.
- In general, cells are most radio-sensitive in the M and G_2 phases, and most radio-resistant in the late S phase.
- The cell cycle time of malignant cells is shorter than that of some normal tissue cells, but during regeneration after injury normal cells can proliferate faster.

14.3 CELL CYCLE AND CELL DEATH

- Cell death of non-proliferating (static) cells is defined as the loss of a specific function.
- Cell death for stem cells and other cells capable of many divisions is defined as the loss of reproductive integrity (reproductive death).

14.4 IRRADIATION OF CELLS

- When cells are exposed to ionizing radiation:
  - First, the standard physical effects between radiation and the atoms or molecules of the cells occur.
  - The possible biological damage to cell functions follows.
- The biological effects of radiation result mainly from damage to the DNA; however, there are also other sites within the cell that, when damaged, may lead to cell death.

14.4 IRRADIATION OF CELLS

- A surviving cell that maintains its reproductive integrity and proliferates almost indefinitely into a large number of progeny is said to be clonogenic.
- The capability of a single cell to grow into a large colony shows that the cell has retained its reproductive integrity.
- In general, to destroy cell function in non-proliferating cells a typical dose of 100 Gy is required, while to destroy proliferative cell capacity requires typically only 2 Gy.

14.4 IRRADIATION OF CELLS

- The sensitive component for radiation-induced cell killing rests in the cell nucleus and not in the cytoplasm.
- When directly ionizing radiation is absorbed in biological material, the damage to the cell may occur in one of two mechanisms:
  - Direct
  - Indirect

14.4 IRRADIATION OF CELLS

14.4.1 Direct action in cell damage by radiation

- In direct action the radiation interacts directly with the critical target in the cell.
- In direct action the atoms of the target itself may be ionized or excited through Coulomb interactions, leading to the chain of physical and chemical events that eventually produce the biological damage.

14.4 IRRADIATION OF CELLS

14.4.1 Direct action in cell damage by radiation

- Direct action is the dominant process in the interaction of high LET particles such as neutrons or alpha particles with biological material.
- In direct action caused by x-ray or gamma ray photons, the photon interaction with an atom in the cell produces a charged particle (electron or positron) which subsequently interacts with the DNA directly.

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

- In indirect action the radiation interacts with other molecules and atoms (mainly water, since about 80% of a cell is composed of water) within the cell to produce free radicals, which can, through diffusion in the cell, damage the critical target within the cell.
- Indirect action can be modified by chemical sensitizers or radiation protectors.

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

- The basic radiochemical reactions that may occur in water molecules disrupted by passage of an ionizing particle are as follows:
  - (1) $H_2O \xrightarrow{h\nu} H_2O^+ + e^- \rightarrow H_2O^+ + e^-_{aq}$
  - (2) $H_2O^+ \rightarrow OH^\bullet + H^+$
  - (3) $H_2O \xrightarrow{h\nu} H_2O^* \rightarrow H^\bullet + OH^\bullet$

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

- The highly reactive species produced in water through the radiochemical reactions are: e^-_{aq}, $OH^\bullet$ and $H^\bullet$.
- These reactive species bring about the indirect radiation damage to biological system by reacting and damaging the molecules in cells.

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

- The free radicals, such as H_2O^+ (water ion) and $OH^\bullet$ (hydroxyl radical), that break the chemical bonds and produce the chemical changes that lead to biological damage are highly reactive molecules because they have an unpaired valence electron.
- About two thirds of the biological damage by low LET radiations (sparsely ionizing radiations), such as x rays and electrons, is due to indirect action and one third is due to direct action.

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

- The steps involved in producing biological damage by the indirect action of x rays are as follows:
  - (1) Primary photon interaction (photoelectric effect, Compton effect, pair production) produces a high energy electron or positron.
  - (2) The high energy light charged particle in moving through tissue produces free radicals in water.
  - (3) The free radicals may produce chemical changes in DNA from the breakage of chemical bonds.
  - (4) The changes in chemical bonds result in biological effects.

14.4 IRRADIATION OF CELLS

14.4.2 Indirect action in cell damage by radiation

For indirect action of x rays the chain of events from the absorption of the incident photon to the final biological damage is as follows:

Incident x-ray photon
⇓ (1) PHYSICS
Fast electron or positron
⇓ (2) PHYSICS
Ion radical
⇓ (3) CHEMISTRY
Free radical
⇓ (4) CHEMISTRY
Breakage of bonds
⇓ (5) BIOLOGY
Biological effect

Typical time scale involved in these 5 steps:

- (1) The physics of the process takes of the order of 10^{-15} s.
- (2) The ion radicals have a lifetime of the order of 10^{-10} s.
- (3) The free radicals have a lifetime of the order of 10^{-5} s.
- (4) The step between the breakage of bonds and the biological effect may take hours, days or years.

14.4 IRRADIATION OF CELLS

14.4.3 Fate of irradiated cells

- Possible outcomes of cell irradiation:
  - No effect.
  - Division delay: The cell is delayed in going through division.
  - Apoptosis: The cell dies before it can divide.
  - Reproductive failure: The cell dies when attempting the mitosis.
  - Genomic instability: There is a delay in reproductive failure.
  - Mutation: The cell survives but contains a mutation.
  - Transformation: The mutation leads to a transformed phenotype and possibly carcinogenesis.
  - Bystander effects: An irradiated cell may send signals to neighboring unirradiated cells and induce genetic damage in them.
  - Adaptive responses: The irradiated cell becomes more radio-resistant.

14.5 TYPE OF RADIATION DAMAGE

14.5.1 Timescale

- The timescale involved between the breakage of chemical bonds and the biological effect may be hours to years, depending on the type of damage.
- If cell kill is the result, it may happen in hours to days, when the damaged cell attempts to divide (early effect of radiation). This can result in early tissue reactions (deterministic effects) if many cells are killed.

14.5 TYPE OF RADIATION DAMAGE

14.5.1 Timescale

- If the damage is oncogenic (cancer induction), then its expression may be delayed for years (late effect of radiation).
- Ionizing radiation has been proven to cause leukemia and has been implicated in the development of many other cancers in tissues such as bone, lung, skin, thyroid, and breast.

14.5 TYPE OF RADIATION DAMAGE

14.5.1 Timescale

- In addition to carcinogenesis (induction of cancer), the late effects of radiation include:
  - Delayed tissue reactions (deterministic effects) such as fibrosis and other reactions mediated by vascular deficiencies.
  - Life span shortening due largely to cancer lethality.
  - Genetic damage, where the effects may be expressed in subsequent generations
  - Potential effects to the fetus.

14.5 TYPE OF RADIATION DAMAGE

14.5.2 Classification of radiation damage.

- The radiation damage to mammalian cells is divided into three categories:
  - Lethal damage, which is irreversible, irreparable and leads to cell death.
  - Sublethal damage, which can be repaired in hours unless additional sublethal damage is added that eventually leads to lethal damage.
  - Potentially lethal damage, which can be manipulated by repair when cells are allowed to remain in a non-dividing state.

14.5 TYPE OF RADIATION DAMAGE

14.5.3 Somatic and genetic effects

- The effects of radiation on the human population can be classified as either somatic or genetic:
  - Somatic effects are harm that exposed individuals suffer during their lifetime, such as radiation induced cancers (carcinogenesis), sterility, opacification of the eye lens and life shortening.
  - Genetic or hereditary effects are radiation induced mutations to an individual's genes and DNA that can contribute to the birth of defective descendants.

14.5 TYPE OF RADIATION DAMAGE

14.5.3 Somatic and genetic effects

- Carcinogenesis expresses itself as a late somatic effect.
- Sources of human data on carcinogenesis:
  - Low level occupational exposure.
  - Atomic bomb survivors in Hiroshima and Nagasaki.
  - Medical radiation exposure of patient:
    - treatment of ankylosing spondylitis with orthovoltage x rays
    - treatment of thyroid abnormalities with radiation
    - radiotherapy in cancer treatment
  - Exposure of staff during medical procedures
    - Early radiologists
    - Early radiation oncologists using brachytherapy

14.5 TYPE OF RADIATION DAMAGE

14.5.4 Stochastic and deterministic (non-stohastic) effect

- The harmful effects of radiation may be classified into two general categories: stochastic and deterministic
  - A stochastic effect is one in which the probability of occurrence increases with increasing dose but the severity in affected individuals does not depend on the dose (e.g., *induction of cancer* and *genetic effects*).
  - There is no threshold dose for effects that are truly stochastic and arise in single cells.

14.5 TYPE OF RADIATION DAMAGE

14.5.4 Stochastic and deterministic (non-stohastic) effect

- The harmful effects of radiation may be classified into two general categories: stochastic and deterministic
  - A deterministic (non-stochastic) effect is one that increases in severity with increasing dose, usually above a threshold dose, and is caused by damage to a population of cells (e.g., *organ dysfunction, fibrosis, lens opacification, blood changes, decrease in sperm count*).

14.5 TYPE OF RADIATION DAMAGE

14.5.5 Acute versus late tissue or organ effects

- An organ or tissue expresses response to radiation damage either as an acute effect or as a late (chronic) effect.
  - Acute effects manifest themselves soon after exposure to radiation and are characterized by:
    - Inflammation
    - Oedema
    - Denudation of epithelia and haemopoietic tissue
    - Haemorrhage

14.5 TYPE OF RADIATION DAMAGE

14.5.5 Acute versus late tissue or organ effects

- An organ or tissue expresses response to radiation damage either as an acute effect or as a late (chronic) effect.
  - Late effects are delayed and may be generic, i.e., caused by absorption of radiation directly in the target tissue, or consequential to acute damage in overlying tissues such as mucosa or the epidermis.
  - Examples of direct late effects are:
    - Fibrosis
    - Atrophy
    - Ulceration
    - Stenosis
    - Intestinal obstruction

14.5 TYPE OF RADIATION DAMAGE

14.5.6 Total body radiation exposure

- The response of an organism to acute total body irradiation exposure is influenced by the combined response to radiation of all organs constituting the organism.
- Depending on the actual total body dose above 1 Gy, the response is described as a specific radiation syndrome:
  - 1 Gy < Dose < 10 Gy — bone marrow syndrome
  - 10 Gy < Dose < 100 Gy — gastrointestinal syndrome
  - Dose > 100 Gy — central nervous system (CNS) syndrome

14.5 TYPE OF RADIATION DAMAGE

14.5.6 Total body radiation exposure

- Sources of human data on specific radiation syndromes:
  - Accidents in industry and research laboratories.
  - Exposure to radioactive fallout from nuclear weapons testing
  - Chernobyl nuclear power plant accident.
  - Exposure of humans to high levels of radiation in Hiroshima and Nagasaki
  - Medical exposure of humans to total body irradiations (TBIs)

14.5 TYPE OF RADIATION DAMAGE

14.5.7 Foetal irradiation

- Between conception and birth the foetus passes through three basic stages of development:
  - Pre-implantation (days 1 to 10)
  - Organogenesis (days 11 to 42)
  - Growth stage (days 43 to birth)
- Radiation is a known teratogen (i.e., causes birth defects).

14.5 TYPE OF RADIATION DAMAGE

14.5.7 Foetal irradiation

- The effects of radiation on the foetus depend on two factors:
  - Dose to the fetus
  - Stage of development at the time of exposure
- An abortion to avoid the possibility of radiation induced congenital abnormalities should be considered only when the fetal dose has exceeded 10 cGy.

14.5 TYPE OF RADIATION DAMAGE

14.5.7 Foetal irradiation

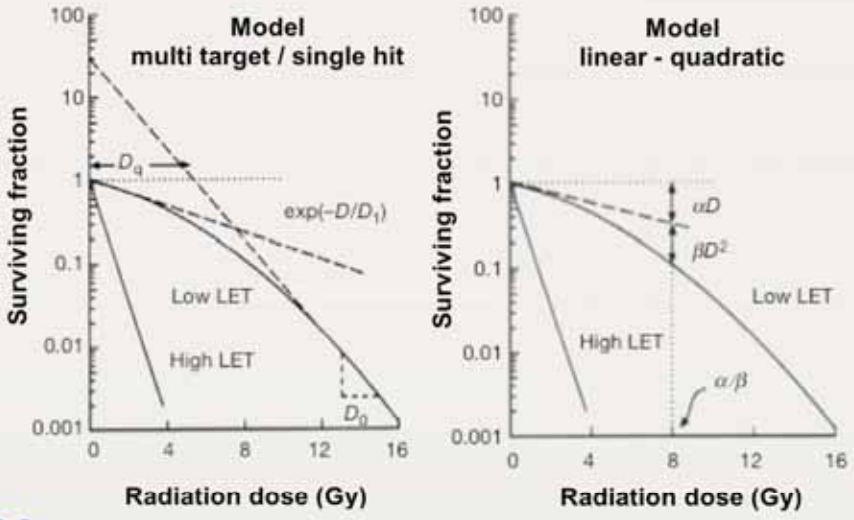
- The principal effects of radiation on a foetus are:
  - Fetal or neonatal death
  - Malformations
  - Growth retardation
  - Congenital defects
  - Cancer induction

14.6 CELL SURVIVAL CURVES

- A cell survival curve (surviving fraction against absorbed dose) describes the relationship between:
  - The surviving fraction of cells, i.e., the fraction of irradiated cells that maintain their reproductive integrity (clonogenic cells)
  - The absorbed dose.
- The cell survival against dose is graphically represented by plotting the surviving fraction $S(D)$ on a logarithmic scale on the ordinate against dose D on a linear scale on the abscissa.

14.6 CELL SURVIVAL CURVES

Typical survival curves for cells irradiated by densely ionizing radiation (high LET) and sparsely ionizing radiation (low LET).



14.6 CELL SURVIVAL CURVES

- Surviving fractions can be measured in vitro or in vivo
- The type of radiation influences the shape of the survival curve.
  - For densely ionizing radiation (high LET) the cell survival curve is almost an exponential function of dose (shown by an almost straight line on a log-linear plot.
  - For sparsely ionizing radiation (low LET) the survival curves show an initial slope followed by a shoulder region and then become nearly straight at high doses.

14.6 CELL SURVIVAL CURVES

- Several factors can make cells less radio-sensitive:
  - Removal of oxygen to create a hypoxic state.
  - Addition of chemical radical scavengers.
  - Use of low dose rates or multi-fractionated irradiation.
  - Synchronization of cells in the late S phase of the cell cycle.

14.6 CELL SURVIVAL CURVES

- Many mathematical models of varying degrees of complexity have been developed to describe the shape of the cell survival curve.
- All models are based on the concept of the random nature of energy deposition by radiation.

14.6 CELL SURVIVAL CURVES

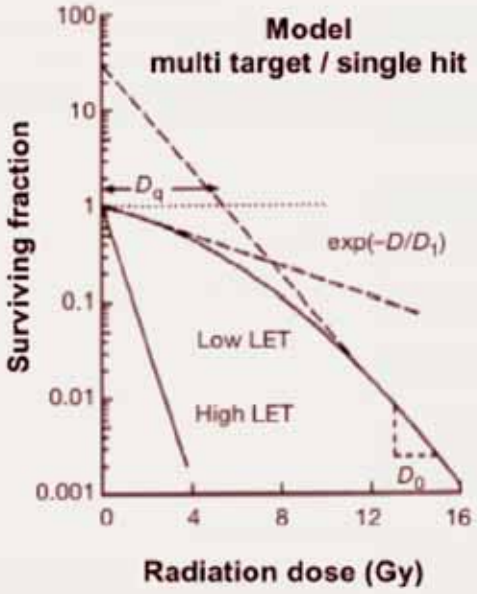
- Currently, the linear-quadratic model is most often used in describing the cell surviving fraction $S(D)$, with the assumption that there are two components to cell kill by radiation (linear and quadratic):

$$S(D) = e^{-\alpha D - \beta D^2}$$

  - α is a constant describing the initial slope of the cell survival curve.
  - β is a smaller constant describing the quadratic component.

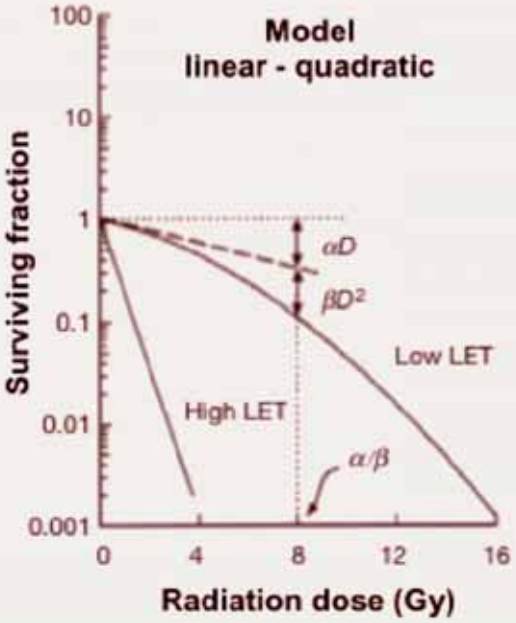
14.6 CELL SURVIVAL CURVES

- The earlier multi-target-single hit model described the slope of the survival curve by:
  - Characteristic dose D_0 (the dose to reduce survival to 37% of its value at any point on the final near exponential portion of the curve).
  - Extrapolation number n (the point of intersection of the slope on the log survival axis).



14.6 CELL SURVIVAL CURVES

- The currently used model for describing the cell survival curve is the linear-quadratic model with constants α and β .
  - The ratio α/β gives the dose at which the linear and quadratic components of cell killing are equal.
  - In this example, the particular α/β ratio results in a characteristic dose of 8 Gy.



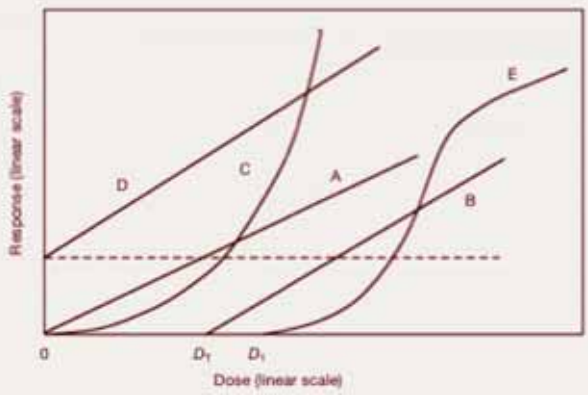
14.7 DOSE RESPONSE CURVES

- A plot of a biological effect observed (e.g., tumour induction or tissue response) against the dose given is called a dose response curve.
- Dose response may refer to:
  - Clonogenic end points, i.e., cell survival.
  - Functional end points.
- Generally, as the dose increases so does the effect.

14.7 DOSE RESPONSE CURVES

- Three types of dose response relationships are known:
  - Linear
  - Linear-quadratic
  - Sigmoid
- Dose response curves may or may not have a threshold dose.
- A threshold dose is the largest dose for a particular effect studied below which no such effect will be observed.

14.7 DOSE RESPONSE CURVES



Dose response curves

(A) Linear relationship with no threshold

(B) Linear relationship with threshold

(C) Linear-quadratic relationship with no threshold (stochastic effects such as carcinogenesis)

(D) Linear relationship with no threshold and the area under the dashed line representing the natural incidence of the effect.

(E) Sigmoid relationship with threshold D1, as is common for deterministic effects in tissues.

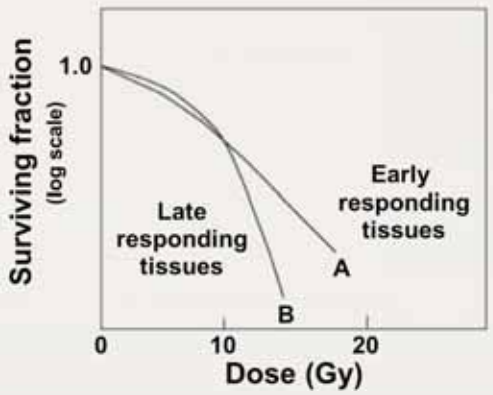
14.7 DOSE RESPONSE CURVES

- The response of tissues or organs to radiation varies markedly, depending on two factors:
  - Inherent sensitivity of the individual cells
  - Kinetics of the population
- With regard to response time two types of tissue are known:
  - Early responding (skin, mucosa, intestinal epithelium).
  - Late responding (spinal cord).

14.7 DOSE RESPONSE CURVES

Properties of cell survival curves:

- For late responding tissues the survival curves are more curved than those for early responding tissues.
- For early effects the ratio α/β is large; for late effects it is small.
- For early effects α dominates at low doses.
- For late effects β has an influence at doses lower than for early responding tissues.
- The α and β components of mammalian cell killing are equal at the following doses:
  - $\alpha/\beta \approx 10$ Gy for early responding tissues
  - $\alpha/\beta \approx 3$ Gy for late responding tissues



14.8 TYPE OF RADIATION DAMAGE

- The effects of radiation on tissue as a function of dose are measured with assays and the measured results are presented in the form of:
  - Cell survival curves
  - Dose response curves.

14.8 TYPE OF RADIATION DAMAGE

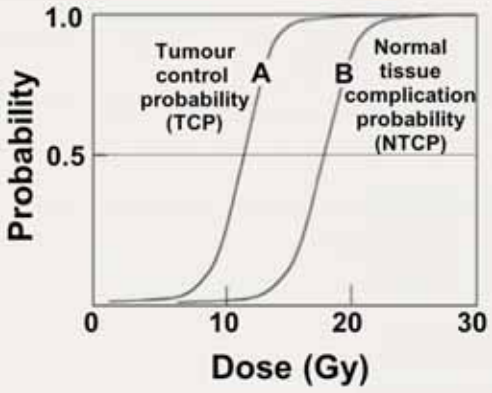
- Three categories of tissue assay are in use:
  - Clonogenic assays measure the reproductive integrity of the clonogenic stem cells in tissue and the measurements result in cell survival curves.
  - Functional assays measure functional end points for various tissues and produce dose response curves.
  - Lethality assays quantify the number of animal deaths after irradiation of the whole animal or of a specific organ with a given dose. The experiments are usually presented with parameter LD_{50}.

14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- Cancer is characterized by a disorderly proliferation of cells that can invade adjacent tissues and spread via the lymphatic system or blood vessels to other parts of the body.
- The aim of radiotherapy is to deliver enough radiation to the tumour to destroy it without irradiating normal tissue to a dose that will lead to serious complications (morbidity).

14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- The principle of radiotherapy is usually illustrated by plotting two sigmoid curves
  - For tumour control probability (TCP)
  - For normal tissue complication probability (NTCP)



14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

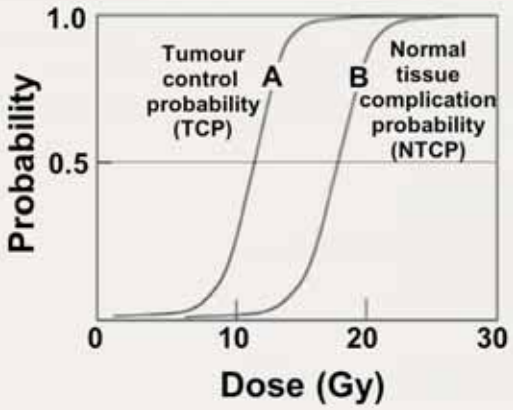
- The optimum choice of radiation dose delivery technique in the treatment of a given tumour is such that it maximizes the TCP and simultaneously minimizes the NTCP.
- For a typical good radiotherapy treatment:
  - TCP ≥ 0.5
  - NTCP ≥ 0.05

14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- The concept of the therapeutic ratio is often used to represent the optimal radiotherapy treatment.
- Therapeutic ratio generally refers to the ratio of the TCP and NTCP at a specified level of response (usually 0.05) for normal tissue.

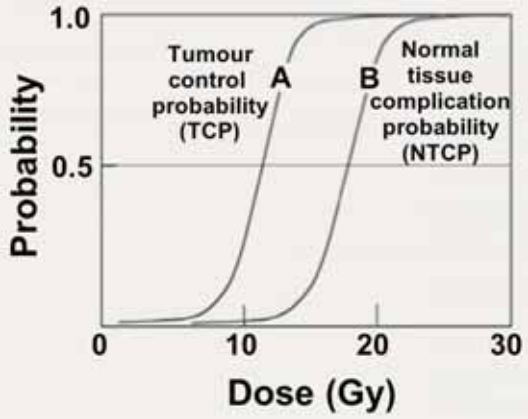
14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- The further the NTCP curve is to the right of the TCP curve:
  - the easier it is to achieve the radiotherapeutic goal
  - the larger is the therapeutic ratio
  - the less likely are treatment complications



14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- The figure shows an ideal situation, in reality the TCP curve is often shallower than the NTCP curve.



14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- The TCP curve for regional control of certain tumours never reaches a value of 1.0 as a result of microscopic or metastatic spread of the disease beyond the primary tumour site.
- It is imperative that the doses to normal tissues be kept lower than the doses to tumours in order to:
  - Minimize treatment complications.
  - Optimize treatment outcomes.

14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

- In modern radiotherapy these objectives are met through:
  - Sophisticated 3-D treatment planning (forward as well as inverse)
  - Accurate target localization
  - Sophisticated dose delivery (conformal, intensity modulated, image-guided).
- In the early days of radiotherapy it was assumed that normal cells were less sensitive to single doses of radiation than tumour cells.

14.9 NORMAL AND TUMOUR CELLS: THERAPEUTIC RATIO

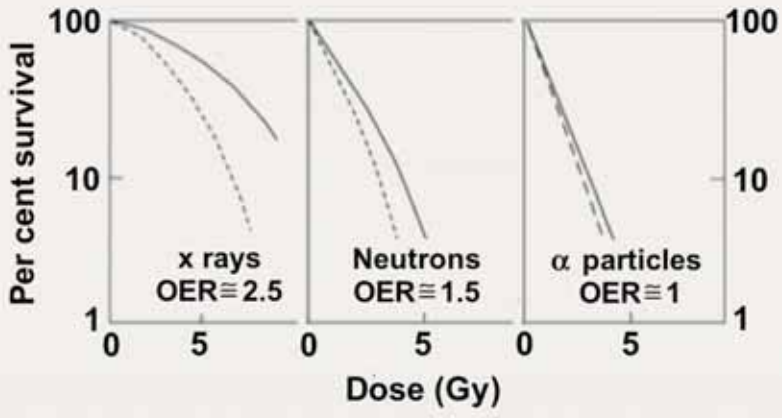
- Currently, it is accepted that both malignant cells and those normal cells responsible for early reactions exhibit similar values for $D_0 \approx 1.3$ Gy, with $\alpha/\beta \approx 10$ Gy.
- It is for late reactions in general that the shoulder on the target cell survival curve is effectively greater than it is for target cells in tumours or early responding tissues with $\alpha/\beta \approx 3$, thus providing a differential that is exploited in hyper-fractionation protocols to spare (reduce) late reactions using small dose fractions.

14.10 OXYGEN EFFECT

- The presence or absence of molecular oxygen within a cell influences the biological effect of radiation: oxygen effect.
- The larger is the cell oxygenation above anoxia, the larger is the biological effect of ionizing radiation; however, a saturation of the effect eventually occurs.

14.10 OXYGEN EFFECT

- The oxygen effect is quite dramatic for low LET (sparsely ionizing) radiation, while for high LET (densely ionizing) radiation it is much less pronounced.



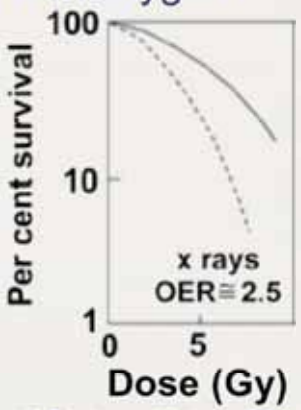
Solid survival curves are for hypoxic cells; dashed survival curves are for well oxygenated cells.

14.10 OXYGEN EFFECT

- The ratio of doses without and with oxygen (hypoxic versus well oxygenated cells) to produce the same biological effect is called the oxygen enhancement ratio (OER).

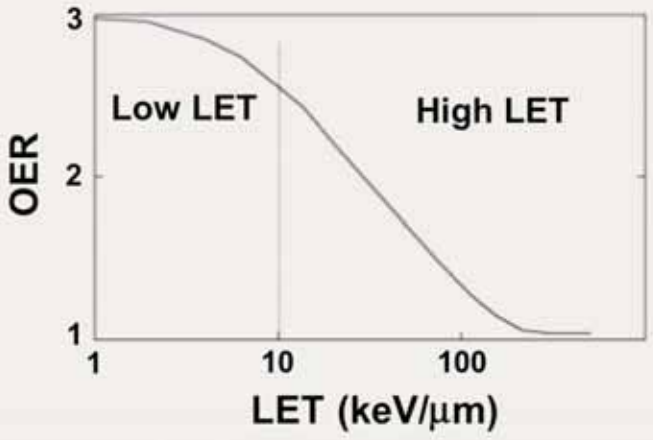
$$\text{OER} = \frac{\text{Dose to produce a given effect without oxygen}}{\text{Dose to produce the same effect with oxygen}}$$

- The OER for x rays and electrons is
  - about 3 at high doses
  - falls to 2 for doses at 1 - 2 Gy.



14.10 OXYGEN EFFECT

- The OER decreases as the LET increases and approaches OER = 1 at LET ≈ 150 keV/μm



14.10 OXYGEN EFFECT

- Cells at the periphery of tumour cords growing around blood vessels become chronically hypoxic because of the consumption of most of the oxygen near the blood vessel.
- The transient closing of blood vessels can also make the whole tumour cord hypoxic for a few minutes at a time.
- Reoxygenation is process by which cells that are hypoxic become oxygenated after irradiation through the killing and removal of oxyc radiosensitive cells from the tumour.

14.11 RELATIVE BIOLOGICAL EFFECTIVENESS

- As the LET of radiation increases, the ability of the radiation to produce biological damage increases.
- The relative biological effectiveness (RBE) compares the dose of test radiation to the dose of standard radiation to produce the same biological effect.
  - Historically, 250 kVp x rays were taken as standard radiation
  - Today cobalt-60 gamma rays are recommended for this purpose.

14.11 RELATIVE BIOLOGICAL EFFECTIVENESS

- The RBE is defined as follows:

$$\text{RBE} = \frac{\text{Dose from standard radiation to produce a given biological effect}}{\text{Dose from test radiation to produce the same biological effect}}$$

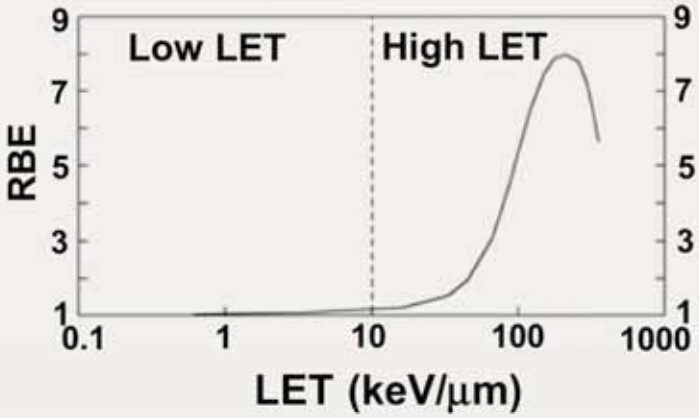
- The RBE varies with:
  - Type of radiation
  - Type of cell or tissue
  - Biologic effect under investigation
  - Dose
  - Dose rate
  - Fractionation

14.11 RELATIVE BIOLOGICAL EFFECTIVENESS

- An increase in the RBE in itself offers no therapeutic advantage unless there is a differential effect making the RBE for normal tissue smaller than that for the tumour, thereby increasing the relative level of tumour cell killing and the therapeutic ratio.

14.11 RELATIVE BIOLOGICAL EFFECTIVENESS

- In general, the RBE increases with LET to reach a maximum RBE of 3 - 8 (depending on the level of cell kill) at LET $\approx$ 200 keV/μm) and then decreases because of energy overkill.



14.12 DOSE RATE AND FRACTIONATION

- For the same radiation dose, radiation delivered at a lower dose rate may produce less cell killing than radiation delivered at a higher dose rate, because sub-lethal damage repair may occur during the protracted exposure.
- As the dose rate is reduced, the slope of the survival curve becomes shallower and the shoulder tends to disappear, since in the linear-quadratic model α does not change significantly but $\beta \rightarrow 0$.

14.12 DOSE RATE AND FRACTIONATION

- The typical dose rates used in radiotherapy are of the order of:
  - 1 Gy/min in standard radiotherapy and high dose rate (HDR) brachytherapy.
  - 0.1 Gy/min in total body irradiation (TBI).
  - 0.01 Gy/min in low dose rate (LDR) brachytherapy

14.12 DOSE RATE AND FRACTIONATION

- Fractionation of radiation treatment so that it is given over a period of weeks rather than in a single session results in a better therapeutic ratio.
- To achieve the desired level of biological damage the total dose in a fractionated treatment must be much larger than that in a single treatment.

14.12 DOSE RATE AND FRACTIONATION

- The basis of fractionation is rooted in 5 primary biological factors called the five Rs of radiotherapy:
  - Radiosensitivity. Mammalian cells have different radio-sensitivities.
  - Repair. Mammalian cells can repair radiation damage.
  - Repopulation. Cells repopulate while receiving fractionated doses of radiation.
  - Redistribution in proliferating cell population throughout the cell cycle phases increases the cell killing from a fractionated treatment.
  - Reoxygenation of hypoxic cells occurs during a fractionated course of treatment, making them more radiosensitive to subsequent doses of radiation.

14.12 DOSE RATE AND FRACTIONATION

- Conventional fractionation is explained as follows:
  - Division of dose into multiple fractions spares normal tissues through repair of sublethal damage between dose fractions and repopulation of cells.
  - The repair of sublethal damage is greater for late responding tissues, the repopulation of cells is greater for early responding tissues.

14.12 DOSE RATE AND FRACTIONATION

- Conventional fractionation is explained as follows (cont.):
  - Fractionation increases tumour damage through reoxygenation and redistribution of tumour cells
  - A balance is achieved between the response of tumour and early and late responding normal tissues, so that small doses per fraction spare late reacting tissues preferentially, and a reasonable schedule duration allows regeneration of early responding tissues and tumour reoxygenation likely to occur.

14.12 DOSE RATE AND FRACTIONATION

- The current standard fractionation is based on:
  - 5 daily treatments per week
  - a total treatment time of several weeks.
- This regimen reflects:
  - the practical aspects of dose delivery to a patient
  - Successful outcome of patient's treatments
  - Convenience to staff delivering the treatment.

14.12 DOSE RATE AND FRACTIONATION

- In addition to the standard fractionation regimens, other fractionation schemes are being studied with the aim of improving the therapeutic ratio:
  - Hyperfractionation uses more than one fraction per day with a smaller dose per fraction (<1.8 Gy) to reduce long term complications and to allow delivery of higher total tumour dose.
  - Accelerated fractionation reduces the overall treatment time, minimizing tumour cell repopulation during the course of treatment.
  - Continuous hyperfractionated accelerated radiation therapy (CHART) is an experimental programme used with three fractions per day for 12 continuous days.

14.13 RADIOPROTECTORS AND RADIOSENSITIZERS

- Some chemical agents may alter the cell response to ionizing radiation, either reducing or enhancing the cell response:
  - Chemical agents that reduce cell response to radiation are called radioprotectors. They generally influence the indirect effects of radiation by scavenging the production of free radicals.
  - Chemical agents that enhance cell response to radiation are called radiosensitizers. They generally promote both the direct and indirect effects of radiation.